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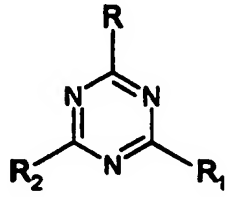
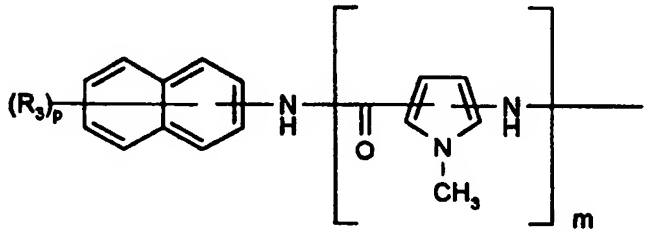
(54) Title: SUBSTITUTED TRIAZINE COMPOUNDS AND THEIR USE IN MEDICINE

(57) Abstract

New triazinic compounds of formula (I) wherein at least one of R, R_1 and R_2 which may be the same or different is a group (A) in which m is an integer of 1 to 6; p is an integer of 1 to 3; each of the R_3 groups, which are the same in each single (A) group, is a free or esterified acid group; and the remaining of R, R_1 and R_2, if any, is a substituent selected from: a halogen atom, a hydroxy group or an amino acid, an ester thereof, a di-, tri-, tetra-, penta- or hexa-peptide or an ester thereof linked to the triazine ring through the amino group; and the pharmaceutically acceptable salts thereof, for use as angiogenesis inhibitors, TNFα-neutralizing activity agents and anti-lentivirus agents, are provided.



(I)



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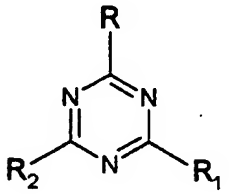
SUBSTITUTED TRIAZINE COMPOUNDS AND THEIR USE IN MEDICINE

The present invention relates to new substituted triazinic compounds, to a process for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

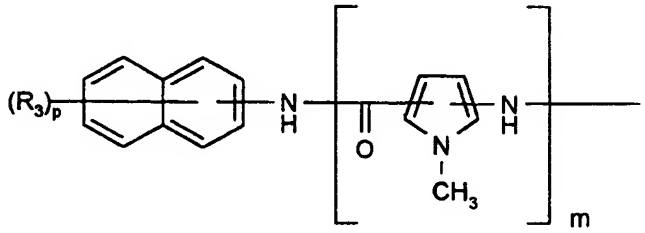
The present invention provides substituted triazinic compounds having the following formula (I)



(I)

wherein

at last one of R, R_1 and R_2 which may be the same or different is a group (A)



(A)

in which m is an integer of 1 to 6;

p is an integer of 1 to 3;

each of the R_3 groups, which are the same in each single (A) group, is a free or esterified acid group; and the remaining of R, R_1 and R_2, if any, is a substituent selected from:

a halogen atom, a hydroxy group or an amino acid, an ester thereof, a di-, tri-, tetra-, penta- or hexa-peptide or an ester thereof linked to the triazine ring through the amino group;

and the pharmaceutically acceptable salts thereof.

A halogen atom is for instance chloro or bromo.

An amino acid is preferably selected from Gly, Ala, Phe, Leu, β-Ala, γ-aminocaproic acid, Val, Tyr, Asp, Glu, Gln, Asn, His and Arg.

A di-, tri-, tetra-, penta-, or hexa-peptide is preferably selected from Phe-Gly, Phe-Phe, Leu-Gly, Val-Ala, Phe-Ala, Leu-Phe, Leu-Ala, Phe-Leu-Gly, Phe-Phe-Leu, Leu-Leu-Gly, Phe-Tyr-Ala, Phe-Gly-Phe, Phe-Phe-Gly, Phe-Leu-Gly-Phe, Gly-Phe-Leu-Gly-Phe, Gly-βAla, Phe-Gly-βAla, Phe-Phe-βAla, Leu-Gly-βAla, Val-Ala-βAla, Phe-Ala-βAla, Leu-Phe-βAla, Phe-Leu-Gly-βAla, Phe-Phe-Leu-βAla, Leu-Leu-Gly-βAla, Phe-Tyr-Ala-βAla, Phe-Gly-Phe, Phe-Phe-Gly-βAla, Phe-Leu-Gly-Phe-βAla and Gly-Phe-Leu-Gly-Phe-βAla.

An ester of an amino acid or an ester of a di-, tri-, tetra-, penta-, or hexa-peptide is for instance an alkyl or aryl-alkyl ester, having a branched or straight alkyl chain. C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters, typically methyl, ethyl, propyl, iso-propyl, butyl, benzyl and phenylethyl esters are more preferred.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bio-precursors of the compounds of the formula (I).

When two or three of R, R_1 and R_2 is a group (A), as defined above, m, p and R_3 in each of said groups may be the same or different.

The free, salified or esterified R_3 groups may be on either or both the phenyl moieties of the naphthalene group.

Examples of R_3 acidic groups, according to the present invention, for instance are those chosen from the group including sulfonic, phosphonic and carboxylic acid groups,

the sulfonic and phosphonic acid groups being the preferred.

Esters of the acids of formula (I) are for instance alkyl and aryl-alkyl esters, having a branched or straight alkyl chain. C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters, typically methyl, ethyl, propyl, iso-propyl, butyl, benzyl and phenylethyl esters are more preferred.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminum hydroxides, or with organic bases, such as lysine, arginine, N-methylglucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethylhexyl)amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, -phenethylamine, N-benzyl- -phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines. Sodium and potassium salts are preferred.

The substituted naphthyl groups are typically 1- or 2-aminonaphthyl groups.

When the naphthyl groups are substituted by three free, esterified or salified acid groups, as defined above, the acid substituents are preferably in the 4,6,8-, 3,6,8-, 3,7,8- positions.

When they are substituted by two free, esterified or salified acid groups, the acid substituents are preferably in the 1,5-, 3,6-, 3,8-, 4,6-, 4,7-, 4,8-, 5,7- or 6,8-positions.

When they are substituted by one free, esterified or salified acid group, the acid substituent is preferably in the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, of course is not linked to the amino position.

The amino and carbonyl groups may be independently linked

to any of the 2 to 5 carbon positions of the pyrrole ring; of course, such groups are not both linked to the same carbon position. The disubstituted pyrroles are typically N-methyl-2,4-disubstituted pyrroles, preferably 1-methylpyrrole-4-amino-2-carbonyl and 1-methylpyrrole-2-amino-4-carbonyl derivatives.

As already said, the invention includes within its scope also the esters and the pharmaceutically acceptable salts of the acids of formula (I).

Only one or both of the two acidic functions of each phosphono $(HO)_2PO$-group are salified and/or esterified.

In the salts of the invention preferably only one of the two acidic functions of each phosphono group is in a salified form, whereas in the esters of the invention both the two acidic functions of each phosphono group are preferably in an esterified form.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly <u>in vivo</u> into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I) in which two or three of R, R_1, and R_2 which may be the same or different is a group (A) wherein p is 2 or 3, m is 1 to 3, and each of the R_3 group, which are the same, is a free or esterified phosphonic or sulfonic acid group; and the remaining of R-R_2, if any, is a substituent selected from halogen and ethyl glycinate;

and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of the invention are:

2,4,6-tris[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-;

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,7-disulfonic acid-4-

amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine;

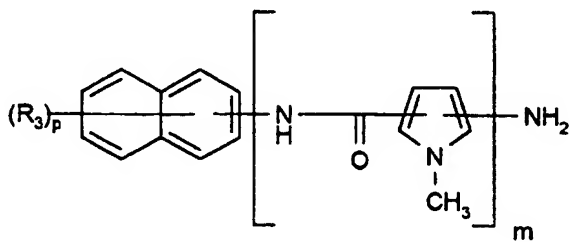
2,4,6-tris(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine;

and the C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters and the pharmaceutically acceptable salts thereof.

Particularly preferred are the methyl, ethyl and benzyl esters and the sodium and potassium salts of the said examples of specific compounds of the invention.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof are hereafter also referred to as "the compounds of the invention" or as "the active agents of the invention".

The compounds of the invention, and the salts thereof can be prepared by a process comprising reacting a compound of formula (II)

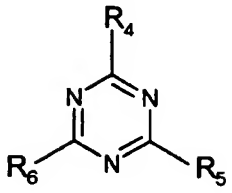


(II)

wherein

m, p and R_3 are as defined above, or a salt thereof,

with a compound of formula (III)



(III)

wherein

at least one of R_4, R_5 and R_6 is chloro and the remaining of R_4-R_6, if any, is as R-R_2 defined above;

and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

A salt of a compound of formula (II) may be a salt with organic or inorganic bases, for example those mentioned above as to the pharmaceutically acceptable salts of the invention, the sodium and potassium salts being the preferred.

The reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III) is an analogy process and can be carried out according to well known methods. Preferably the reaction may be carried out at a molar ratio of compound (II) or a salt thereof: compound (III) from about 1 : 0.2 to about 1 : 4.

The reaction is preferably performed in an organic solvent, such as dichloromethane, dichloroethane, chloroform, toluene, or dimethylsulphoxyde, dimethylformamide, dimethylacetamide, hexamethylphosphoramide, or their

aqueous mixtures, or in water/acetone, water/dioxane, water/toluene or water/dichloromethane mixtures, in the presence of either an organic base such as triethylamine, diisopropylethylamine or pyridine or an inorganic base such as sodium bicarbonate or sodium acetate or a convenient buffer as known in the art. The reaction temperature may vary from about -10°C to about 150°C and the reaction time from about 1 to about 24 hours.

The compounds of formula (I) prepared according to the above described procedures may be purified by conventional methods such as by silica gel, alumina or reversed phase column chromatography, and/or by recrystallization from organic solvents such as lower aliphatic alcohols or dimethylformamide or their mixtures or in water containing mixtures.

Analogously, esterification or salification of an acid of formula (I) can be carried out by known methods in the art.

The compounds of formula (II) are known products and can be obtained according to PCT/EP91/00014 or to PCT/EP95/00444.

Compounds of formula (III) are known products or may be easily obtained according to known methods from known products.

For instance a compound of formula (III) can be obtained starting from 2,4,6-trichloro-1,3,5-triazine according to known methods in organic chemistry.

PHARMACOLOGY

The new compounds of the present invention, are angiogenesis inhibitors, as shown, e.g., by the fact that they have been found to be active in the chorioallantoic membrane test, according to the Folkman's method [Nature, 297, 307 (1982)]. Therefore

the compounds of the present invention are useful in treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example, in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In particular, in the cancer therapy the compounds of the invention can be administered alone or in association with antitumor agents such as doxorubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin or mitomycin.

The compounds of the present invention have also been found to be endowed with TNFα-neutralising activity and therefore they can be employed in humans for prophylactic and/or therapeutic use in any disease state in which TNFα is known to play a detrimental role. Typically such disease states are cachexia, septic shock, graft-versus-host disease, AIDS, cerebral malaria, rheumatoid arthritis. The TNFα-inhibiting activity of the compounds according to the present invention is proven, for instance, by the fact that they are active in inhibiting the cytotoxicity activity of human TNFα on untreated mouse LM cells.

Accordingly, the compounds of the invention can be used as angiogenesis inhibitors and/or as TNFα-neutralising activity agents. The compounds of the invention can thus be used in the preparation of a medicament for use in the treatment of angiogenesis and/or for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role. In these therapeutical applications the compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously,

topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.5 to about 250 mg pro dose 1-4 times a day.

Moreover, the compounds of the present invention have been found to act directly as anti-lentivirus agents, in particular against Human Immunodeficiency Virus (HIV).

For instance, the representative compounds of the invention 2,4,6-tris[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt have been found to be active in the biological test described in J. Natl. Cancer Inst. 81, 557-586 (1989). A uman patient suffering from lentivirus infection can thus be treated by a method comprising administering thereto an effective amount of one of the compounds of the invention. In this way, the compounds of the invention can be used to treat an infection attributable to a lentivirus, in particular a human immunodeficiency virus, especially HIV-1 or HIV-2.

The compounds of the invention can also be used in the preparation of a medicament for use in the treatment of a human patient suffering from lentivirus infection. The said medicament may be for use as an anti-lentivirus agent, for

example an anti-HIV-1 or -HIV-2 agent. The said medicament may also be for use in ameliorating the symptoms of lentivirus-induced disease in a human patient suffering from lentivirus infection.

In particular the compounds of the invention can be used in the preparation of an agent to be used in the treatment of a human patient who is seropositive diseased or pathological as a result of infection with a lentivirus, in particular HIV, or who is suffering from induced disease, e.g., lymphoadenopathy syndrome (LS), AIDS-related complex (ARC), AIDS or Kaposi's sarcoma. The condition of a human patient can thus be ameliorated or improved.

In these therapeutical applications the compounds of the invention can be administered by usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection or infusion being preferred. The dosage depends on the age, weight and condition of the patient and on the administration route.

A suitable dosage for the compounds of the invention, for example 2,4,6-tris[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine or a pharmaceutically acceptable salt thereof, for administration to adult humans is from about 0.4 to about 250 mg per dose 1-4 times a day.

The compounds of the invention may be used in a method of treatment of the above mentioned pathological conditions comprising both separate and substantially contemporaneous administration of a composition containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing

different pharmaceutically active agents. The present invention therefore further provides products comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a second active agent as a combined preparation for separate, simultaneous or sequential use in treating a human patient suffering from lentivirus infection, in particular infection with HIV. The second active agent is typically a drug that affects the pathogenesis of HIV-induced diseases.

For example, the compounds of the invention may be employed with various active agents, in particular those that affect reverse transcriptase, antimicrobial and antitumor agents or a mixture of two or more thereof. Drugs of interest include non-nucleoside reverse transcriptase inhibitors, e.g. nevirapine; nucleoside derivatives, e.g. zidovudine and didanosine; acyclovir; ribavirin; ascorbic acid; protease inhibitors; cytokine, e.g. IL-1, IL-2, IL-3 or IL-4; growth factors; interferons, e.g. alpha- or gamma-interferon; antitumor agents, e.g. doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin and mitomycin; immunomodulating agents, in particular immunostimulants, gamma globulin, immune globulin and monoclonal antibody products, antibiotics and antimicrobial products.

Typically, the antimicrobial agents may include a penicillin in conjunction with an aminoglycoside (e.g. gentamycin, tobramycin).

However several well additional agents, e.g. cephalosporin, can be utilised.

The administration dosage of these drugs will vary, depending upon the disease status of the individual. The

dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

The pharmaceutical composition used in the invention may comprise a compound of formula (I) or pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers. The pharmaceutical compositions are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions. Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose, polyvinyl-

pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The following examples illustrate but do not limit the invention.

Example 1

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt [PNU 157015, compound(I), R_3=SO_3H, m=2, p=2].

A solution of 2,4,6-trichloro-1,3,5-triazine (35 mg, 0.189 mmol) in acetone (5 ml) was added to a stirred, ice-cooled suspension of 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid disodium salt hydrochloride (237 mg, 0.378 mmol) in water (10 ml). A first equivalent of $NaHCO_3$ (31.7 mg, 0.378 mmol) dissolved in water (1 ml) was added dropwise at 0-5°C and a second equivalent (31.7 mg) was then added at room temperature. The whole was stirred at RT for 2 h. The solvent was removed under reduced pressure and the residue purified by reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:CH_3CN 80:20. The product containing eluate was concentrated under reduced pressure, treated with 50 ml of acetone and stirred for 30 min. The solid was filtered, washed with acetone and

vacuum-dried to give the title compound as a yellow solid (122 mg).

(-)FAB MS (m/z): 1270 $(M-Na)^-$

^1H NMR (DMSO-d_6, T=75°C): δ 6.8-7.3 (m, 4H); 7.82 (d, 1H); 7.89 (dd, 1H), 8.02 (s, 1H); 8.28 (d, 1H); 8.98 (s, 1H); 9.70 (bs, 1H); 9.73-9.97 (two s, 2H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine hexasodium salt;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt; and

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine tetrasodium salt.

Example 2

2-(N-[ethyl glycinate])-4,6-dichloro-1,3,5-triazine

[compound (III)]

A solution of ethyl glycinate hydrochloride (5.0 g, 35.8 mmol) and $KHCO_3$ (3.58 g, 35.8 mmol) in H_2O (15 ml) and acetone (10 ml) was added to an ice-cooled, stirred mixture of 2,4,6-trichloro-1,3,5-triazine (6.61 g, 35.8 mmol), crushed ice (25 g) and acetone (50 ml). Additional $KHCO_3$ (3.58 g, 35.8 mmol) was added in small portions in 1 h. The ice-bath was then removed and the whole was stirred at room temperature for 6 h. The organic layer was separated and treated with 75 ml of water. The precipitated crystalline white solid was filtered, washed with H_2O and dried at 40°C under vacuum for 1 h to give the title compound (5.18 g).

^1H NMR (DMSO-d_6): δ 6.8 (bt, 1H); 4.2-4.3 (d + q, 4H); 1.3 (t, 3H).

Example 3

4,6-Bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt [PNU 157914, compound(I), $R_3=SO_3H$, m=2, p=2]

A solution of 2-(N-[ethyl glycinate])-4,6-dichloro-1,3,5-triazine of Example 4 (95 mg, 0.379 mmol) in acetone (5 ml) was added to a stirred suspension of 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid disodium salt hydrochloride (238 mg, 0.379 mmol) in H_2O (10 ml). A solution of $NaHCO_3$(64 mg, 0.758 mmol) in H_2O (3 ml) was added dropwise and the whole was stirred at RT for 3h.

A second equivalent of 7-({4-[(4-amino-1-methylpyrrole-2-

carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino) naphthalene-1,3-disulfonic acid disodium salt hydrochloride (238 mg, 0.379 mmol) was then added, followed by addition of $NaHCO_3$ (64 mg, 0.758 mmol) in H_2O (3 ml) and the whole was stirred at 80-90 °C for 4 h.

The volatiles were evaporated and the residue purified by reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:CH_3CN 85:15. The product containing eluate was concentrated under reduced pressure, treated with 100 ml of acetone and stirred for 30 min. The solid was filtered, washed with acetone and vacuum-dried at 35°C to give the title compound as a white solid (288 mg).

(-)FAB MS (m/z): 1337 $(M-Na)^-$

^1H NMR (DMSO-d_6, T=50°C): δ 1.16 (t, 3H); 4.14 (m, 4H); 3.88 (s, 12H); 6.8-7.5 (m, 8H); 7.82 (d, 2H); 7.89 (dd, 2H); 8.00 (m, 2H); 8.25 (d, 2H); 8.96 (m, 2H); 9.6 (bs, 2H); 9.81, 10.09 (two s, 4H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine hexasodium salt;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt; and

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt.

Example 4

2,4,6-Tris[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt [PNU 157666, compound (I), $R_3=SO_3H$, m=2, p=2].

A solution of 2,4,6-trichloro-1,3,5-triazine (70 mg, 0.378 mmol) in acetone (5 ml) was added to an ice-cooled, stirred suspension of 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid disodium salt hydrochloride (475 mg, 0.757 mmol) in H_2O (15 ml). A solution of $NaHCO_3$ (64 mg, 0.757 mmol) in H_2O (2 ml) was added dropwise, the ice-bath removed and a second equivalent of $NaHCO_3$ (64 mg, 0.757 mmol) in H_2O (2 ml) was added at RT. After stirring for 2 h, 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid disodium salt hydrochloride (238 mg, 0.378 mmol) was added and the reaction mixture warmed to 90°C. A third equivalent of $NaHCO_3$ (64 mg, 0.757 mmol) in 2 ml of H_2O was then added and the whole stirred at 90°C for 5 h.

The reaction mixture was diluted with H_2O to 50 ml, the acetone evaporated under reduced pressure and the

precipitated gel was filtered, washed with H_2O and acetone and dried to give a brown solid. Further purification by reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:CH_3CN 80:20 afforded the title compound as a yellow solid (191 mg).

^1H NMR (DMSO-d_6, T=75°C): δ 3.89, 3.90 (two s, 6H); 6.89, 7.20, 7.28 (three d, 3H); 7.37 (bs, 1H); 7.81 (d, 1H); 7.88 (dd, 1H); 8.01 (s, 1H); 8.28 (d, 1H); 8.72 (bs, 1H); 8.98 (d, 1H); 9.64, 9.97 (two s, 2H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

2,4,6-tris[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt;

2,4,6-tris[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt;

2,4,6-tris[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine nonasodium salt;

2,4,6-tris[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt;

2,4,6-tris[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine hexasodium salt;

2,4,6-tris{2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine hexasodium salt;

2,4,6-tris{2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine

hexasodium salt;

2,4,6-tris{2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine nonasodium salt;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine hexasodium salt;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine hexasodium salt; and

2,4,6-tris(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine nonasodium salt.

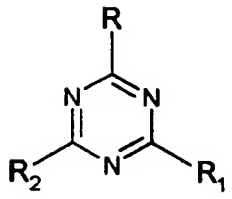
Example 5

Intramuscular injection 30 mg/ml.

An injectable pharmaceutical preparation can be manufactured by dissolving 30 g of 4,6-Bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine tetrasodium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

CLAIMS

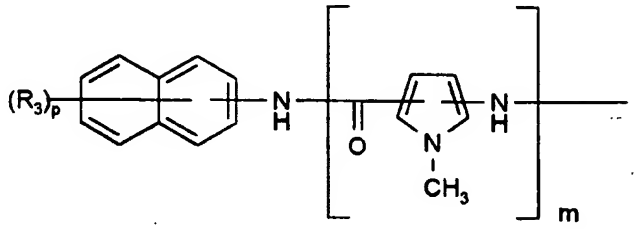
1. A triazinic compound of formula (I)



(I)

wherein

at least one of R, R_1 and R_2 which may be the same or different is a group (A)



(A)

in which m is an integer of 1 to 6;

p is an integer of 1 to 3;

each of the R_3 groups, which are the same in each single (A) group, is a free or esterified acid group; and the remaining of R, R_1 and R_2, if any, is a substituent selected from:

a halogen atom, a hydroxy group or an amino acid, an ester thereof, a di-, tri-, tetra-, penta- or hexa-peptide or an ester thereof linked to the triazine ring through the amino group; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to claim 1, wherein each R_3 acid group is independently chosen from sulfonic, phosphonic and carboxylic acid groups.

3. An ester of a compound of formula (I), as defined in claim 1, wherein said ester is a C_1-C_6 alkyl or a phenyl-

C_1-C_6 alkyl ester.

4. A compound of formula (I), as defined in claim 1, in which two or three of R, R_1, and R_2 which may be the same or different is a group (A) wherein p is 2 or 3, m is 1 to 3, and each of the R_3 group, which are the same, is a free or esterified phosphonic or sulfonic acid group; and the remaining of R-R_2, if any, is a substituent selected from halogen and ethyl glycinate; or a pharmaceutically acceptable salts thereof.

5. A compound selected from:

2,4,6-tris[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

2,4,6-tris[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-(N-[ethyl glycinate])-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

4,6-bis[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-;

4,6-bis[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-;

4,6-bis[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]-2-chloro-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris{2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}-1,3,5-triazine;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine;

2,4,6-tris(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine; and

2,4,6-tris(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)-1,3,5-triazine;

or a C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl ester, or a pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active compound, a compound of formula (I) according to

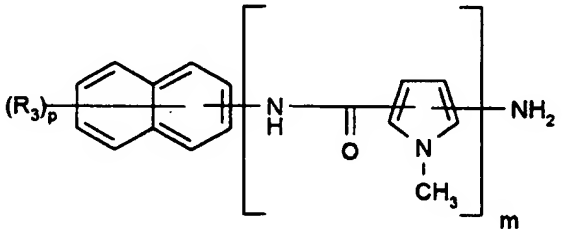
claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as angiogenesis inhibitor.

8. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as TNFα-neutralizing activity agent.

9. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as anti-lentivirus agent.

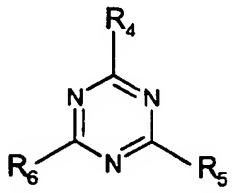
10. Process for the preparation of a compound of formula (I), as defined in claim 1, or a salt thereof, said process comprising reacting a compound of formula (II)



(II)

wherein

m, p and R_3 are as defined in claim 1, or a salt thereof, with a compound of formula (III)



(III)

wherein

at least one of R_4, R_5 and R_6 is chloro and the remaining of

R_4-R_6, if any, is as R-R_2 defined in claim 1;

and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 98/03453

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/34 A61K31/53 C07D403/12 C07D403/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26950 A (PHARMACIA SPA ;MONGELLI NICOLA (IT); BIASOLI GIOVANNI (IT); LOMBAR) 6 September 1996 see claims 1,8,9 ---	1-10
A	WO 91 10649 A (ERBA CARLO SPA) 25 July 1991 cited in the application see abstract ---	1-10
A	WO 95 23806 A (PHARMACIA SPA ;MONGELLI NICOLA (IT); GRUGNOLA ANGELO (IT); LOMBARD) 8 September 1995 cited in the application see abstract ---	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1998	25/09/1998

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